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A CLINICAL STUDY OF THE THERAPEUTIC VALUE OF THE CALCIUM SALTS IN GASTRIC TETANY, WITH AN ANATOMICAL REPORT ON THE PARATHYROID BODIES.[1]

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Recent researches tend to show that there is an intimate relation between the various forms of tetany and an insufficiency of the parathyroid glands; they also strongly suggest that there is an equally direct and intimate relation between disturbances of the calcium contents of the tissues of the body and tetany; and, finally, that the secretion of the parathyroid bodies exerts in an as yet imperfectly understood way a controlling influence upon calcium metabolism. Numerous researches have shown the moderating effect of the calcium salts upon the hyperexcitability of the central nervous system, and the recent noteworthy study by MacCallum and Voegtlin[2] has demonstrated the controlling influence of these salts upon the spasm of experimental tetany. The results observed by them have suggested the probable therapeutic value of the calcium salts in the various forms of human tetany.

Recently an opportunity has been afforded in the Presbyterian Hospital for a study of the effect of the calcium salts in a case of gastric tetany, and of the parathyroid bodies after death. The case is of much interest in view of the rarity of that form of gastric tetany associated with dilatation of the stomach and stagnation of its contents, of which it is an example; in the severity of the tetanic symptoms; in the prompt inhibitory effect upon the spasms of the calcium salts artificially introduced directly into the blood stream; and, finally, in the findings at autopsy.

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[1] Read at a meeting of the Association of American Physicians, Washington, D. C., May 11 and 12, 1909.

[2] On the Relation of Tetany to the Parathyroid Glands and to Calcium Metabolism, Jour. Exp. Med., 1909, xi, 118.

A male, aged thirty-three years, was received in my wards in the Presbyterian Hospital on October 25, with the diagnosis of gastric tetany by my interne Doctor Vaughan, a diagnosis fully confirmed on examination of the patient. The family and personal histories, briefly, are as follows: Both parents died of pulmonary tuberculosis. The patient at times has been a heavy drinker, and especially has been a large consumer of beer. There is a history of gastric symptoms from early in 1905, at which time he was admitted to Bellevue Hospital suffering apparently from an acute gastritis of alcoholic origin; he was discharged relieved of his symptoms. A year later he was again admitted on account of a severe gastric hemorrhage following a drinking bout. A diagnosis of duodenal ulcer was made. On discharge from the hospital, and up to the date of the illness for which he was admitted to the Presbyterian Hospital, he suffered from much epigastric distress, flatulence, and frequent vomiting. He states that occasionally as much as "a gallon of green fluid" was vomited, but at no time any blood. The night before admission to my wards the patient states that he drank copiously of aërated water, nothing alcoholic. He went to bed feeling well, slept, but awoke several hours later with severe cramps in the legs and arms. He was unable to move them, but felt no pain beyond a drawn and tense feeling in the cramped muscles. He called for assistance with difficulty, as his tongue and jaws were stiff. His abdomen was distended, and he vomited several times. He sweated profusely. He was very restless. Later his affected muscles became tender and were painful. The cramps and stiffness in no way relaxed up to the time of admission.

Examination on Admission. Patient is poorly nourished; looks ill. Is unable to speak intelligibly. Is extremely restless. Temperature (rectal), 101°. Pulse, 100 and of poor quality, regular in rhythm. Blood pressure, systolic, 112 mm. Respirations, 80. The attention is at once attracted to the abdomen and to the presence of tetanic symptoms. The contour of a dilated and distended stomach is easily appreciable. The lower outline reaches a point 10 cm. below the umbilicus in the median line, and to the right the distention reaches well beyond the parasternal line. Succussion sounds can be produced readily over the whole of the distended area. Both legs are held straight and stiff, the feet in extreme extension, the toes in plantar flexion. The muscles of the calf of legs are hard, tense, and drawn. The spasm is continuous, but pressure on the nerve trunks and bloodvessels increases, if possible, the severity of the spasm (Trousseau's sign), and the same phenomenon obtains on tapping over the motor nerves supplying the affected muscles (Chvostek's sign). The forearms are flexed at a right angle on the arms, the wrists flexed to an extreme degree and cannot be extended, the fingers flexed at right angles at the metacarpophalangeal articulations and held rigidly straight in adduction, the thumb tightly against index finger—not drawn into palm. The spasms are continuous, but, as in the case of the lower extremities, they can be increased both by Trousseau's and Chvostek's methods. The tendon reflexes appear to be about normal in both upper and lower extremities. There are continuous twitchings of the muscles of the face, which are increased by tapping over the course of the motor trunks. A slight degree of trismus is present. The musculature of the trunk is free from spasm, and it cannot be excited by mechanical irritation of the motor nerves or the muscles. The tachypnœa is striking, the respirations, as previously stated, being 80.

The stomach was at once washed out and a large quantity of greenish ill-smelling fluid was recovered. A few hours subsequent to the lavage the spasms of the upper extremities were entirely relieved, but there was no intermission in those of the lower.

October 26. The spasms of the upper extremities are again present and are continuous, and there has been no intermission in those of the lower extremities. In spite of lavage twice used in the past twenty-four hours the patient has vomited several times, 80 ounces in all; the vomited matter a greenish fluid. The patient has not voided urine since admission, and catheterization recovered only 6 ounces of urine, of specific gravity 1016, containing a trace of albumin, no glucose, a trace of indican, and a few hyaline and granular casts. Subcutaneous clyses, 1000 c.c. of a normal salt solution, were ordered to relieve, if possible, the evident dehydration of the body tissues. The temperature fell gradually during the day to 97.5° at midnight; the respirations to 20 to 24. Blood examination: Red cells, 4,910,000; white cells, 13,500; hemoglobin, 75 per cent.; color index, 0.7; polymorphonuclears, 89 per cent.; large and small lymphocytes, 9.3 per cent; transitionals, 1.7 per cent.

October 27. There has been no appreciable diminution in the spasms of the extremities, which are still continuous. In addition to lavage and subcutaneous clyses, one-half grain of a parathyroid extract, furnished by Dr. Beebe, was directed to be given three times daily by the mouth, and caffeine as a heart stimulant. The temperature has been subnormal throughout the day. In view of the pulmonary signs present, von Pirquet's tuberculin test was tried, with negative results.

October 28 (A.M.). The patient was extremely restless and irrational in the early part of the night, but after lavage and a subcutaneous clysis of 2000 c.c. of salt solution, slept quietly, with a partial relief of the spasms of the upper extremities, but with continued extensor spasm of the muscles of the legs. During the day the spasms in the upper extremities have again been present, and there has been no intermission in those of the lower extremities. Patient very restless and irrational. In addition to the parathyroid extract, 2 grams of calcium lactate in 1200 c.c. of normal salt solution was directed to be given intravenously. The immediate effect was to quiet the great restlessness of the patient, and a few hours later there was a marked diminution in the degree of spasm in the upper extremities, and for the first time since admission, in the lower extremities. The temperature rose slightly to 100° before the use of the calcium salt, and did not rise above this after its administration. Pulse, 80 to 96; respirations, 20 to 24.

October 29 (A.M.). The patient slept quietly the greater portion of the night. There is no spasm of the upper extremities and only slight spasm (extensor) of the legs. The electrical reactions were tested for the first time and were not found to be increased. (P.M.) Four grams of calcium lactate in 1300 c.c. of normal salt solution was given intravenously. The patient fell asleep during its administration, and for the first time since admission he became entirely relaxed. Temperature, 99.5° to 100.5°; respirations, 20.

October 30. The patient slept quietly during the night. The upper extremities are free from spasm. Late in the day slight spasm of the extensor muscles of the legs was noted. Tapping over the branches of the facial nerve still elicits slight spasm in the muscles of its distribution. This can be produced only after several moments of mechanical irritation, in marked contrast to the almost instantaneous response obtained before the first administration of the calcium salt. Four grams of calcium lactate in 1000 c.c. of normal salt solution was again given intravenously in the late afternoon. Temperature, normal. Pulse, 80 to 84; respirations, 20.

October 31. The patient slept quietly with an entire absence of spasm. Both upper and lower extremities are free from spasm, but there is slight rhythmic movement of the forearms, about 60 times a minute. The patient's mind is quite clear for the first time, and he takes an interest in all that is done for him and asks intelligent questions in regard to its purpose. The pulse has ranged from 82 to 96. The temperature (rectal) has been normal. Respirations, 20 to 24. White cells, 9900. Calcium lactate in 1000 c.c. normal salt solution was given.

November 1. The rhythmic movements of the forearms have disappeared. Spasm is entirely absent in the lower extremities. Upper extremities: From time to time the hand is momentarily flexed on forearm at intervals of about five seconds. Mechanical irritation of the nerve trunks does not increase this phenomenon. The calcium salt was omitted and a nucleoproteid preparation of the parathyroid, furnished by Dr. Beebe, was injected deep into the gluteal region twice in the twenty-four hours. Pulse, 80 to 95 during day. Temperature, slightly subnormal. Respirations, 20 to 24.

November 2. The patient slept quietly during the night. The spasms of the muscles of the forearms have increased and there is very considerable tremor of the hands. There is also some tremor of the muscles of the chin. Pulse, 84 to 96. Temperature, subnormal during the day. Respirations, 20 to 24. In view of the increase in the spasms, in addition to the parathyroid preparation, 4 grams of calcium lactate in 1000 c.c. of normal salt solution was again given intravenously.

November 3. The patient is entirely relaxed and no spasm can be elicited by mechanical irritation of the nerve trunks in either upper or lower extremities or in the muscles of the face. Considerable tremor of the hands is present, however. The patient's general condition is not as good. Hiccough is present. The pulse is of poor force, 80 to 100 during the day. Temperature, subnormal. Respirations, 20. Four grams of calcium lactate in salt solution was given intravenously. From this date the calcium salts were discontinued and no other medication was used. There was no further spontaneous spasm, and it could not be excited by mechanical means. The patient's mind remained entirely clear, he was interested in measures taken for his relief, and was able partially to sit up in bed. There was little or no change in the temperature, pulse, and respirations from those last noted. Three days later, without the occurrence of other symptoms, the heart rather suddenly failed, and death followed speedily.

That portion of the clinical history which especially relates to the tetanic symptoms and to the effect secured by the administration of the calcium salts has been selected for detailed report. Other portions of the history will be given only in outline.

It was found impossible to nourish the patient by means of the stomach. Vomiting was frequent on each attempt, in spite of copious and frequent lavage. Nutriment introduced after lavage by means of the stomach tube, although sometimes retained, was recovered later by the tube in like amounts, showing no signs of gastric digestion—only decomposition processes. Nutrient enemas were only exceptionally retained. There was almost complete anuria for the first twenty-four hours and until abundant subcutaneous clyses of salt solution had been given. Later, the urine either was voided involuntarily or was recovered by catheterization. The scanty fluid stools were mostly involuntary.

Although the tetanic symptoms obviously could be controlled by the continued administration of the calcium salts, it was equally apparent that the patient would slowly die of inanition unless the evident gastric stenosis could be relieved by operation. In consultation, however, my late colleague, Dr. McCosh, decided against surgical intervention, on the ground that any operation would be immediately fatal.

Autopsy, sixteen hours postmortem, by Dr. Opie. The body is that of an emaciated man 160 cm. in length. Over the inner surface of the left elbow and on the right arm there are ecchymoses. The subcutaneous fat is present in very small amount, and has a deep yellow color. The peritoneal cavity contains no accumulation of fluid; fat has almost wholly disappeared from omentum. The greater curvature of the stomach is 16 cm. below the ensiform cartilage in median line. The stomach extends 9 cm. to the right of the midline, and is in contact with the ribs on the left side. The lesser curvature of the stomach in the midline is 6 cm. below the ensiform cartilage. The spleen is firmly adherent to the lateral abdominal wall. The stomach has fallen considerably, and above the lesser curvature the entire head and greater part of the pancreas is visible. The lungs are emphysematous and meet in the median line; a few adhesions bind each apex to the chest wall. The pericardial cavity contains about 10 c.c. of clear fluid. The appendix arises from the inner surface of the cecum, passes inward, and lies with the tip over the pelvic brim. It is possible to pass one finger with difficulty through the foramen of Winslow.

The stomach measures 25 cm. transversely and 8.5 cm. vertically at the cardiac end. Pyloric half is almost tubular and is 5 cm. in diameter. On opening the stomach it was found to contain several hundred c.c. of bright yellow fluid, from which a sediment settles. Adherent to the mucosa is mucus. The mucous membrane is thickened, the rugæ are prominent, and the surface has a homogeneous, deep red color. The wall of the stomach is thickened by hypertrophy of its muscular layer to about 4 mm. The duodenum immediately beyond the pylorus is bent backward and held in contact with the stomach by adhesions for a distance of about 1 cm. Gentle separation of the adhesions exposes a perforation, from which gastric contents escape. It is found impossible to pass a finger from the stomach through the pylorus into the duodenum, obstruction being in a large part due to the bend just described. Immediately below the pylorus in the mucous membrane of the duodenum there is a depressed scar, 0.25 x 1 cm., partially encircling the duodenum. At the upper angle of this area is a deeper ulceration, in diameter not more than 7 mm.; the surface here is black and eroded, and the partial perforation mentioned above allows the passage of a small probe. There is thick fibrous tissue immediately about the ulcer, but no marked induration. The duodenum is somewhat injected, but otherwise normal. The pancreas is normal. The heart weighs 255 grams. The organ is small; the muscle is firm and brownish in color. The aortic valve is normal; there is slight thickening of the free edge of the mitral valve; there are several minute nodular projections. The pulmonary and tricuspid valves are normal. The coronary arteries are smooth.

The left lung is voluminous, and abundant fluid escapes from the cut surface. Throughout a large part of the upper lobe is scattered gray nodules partly caseous; there are several larger nodules 1.5 cm. across, and cavity formation has occurred in the centre of a caseous area. Right lung is much more voluminous than the left; tubercles are much more numerous in the upper lobe, and there occur several small cavities similar to the cavity in the left lung; it is in direct communication with a bronchus. The uppermost 2 cm. of the apex is almost entirely consolidated by tuberculous nodules. The lower lobe contains sparsely scattered tubercles; in large part it is firm and is partially consolidated by scattered areas of homogeneous, deep red color, though nowhere is it entirely airless. The liver weighs 1450 grams. The organ is firm and deep red; the mottling is indistinct. Gall-bladder is contracted and contains a small amount of viscid bile. The spleen is not enlarged; it measures 11 x 7.5 x 4.5 cm. It is very firm, and has a homogeneous, deep red color; the Malpighian bodies not well seen. The kidneys weigh 310 grams together. They resemble each other closely; the capsule is removed easily, leaving a red surface in which there are a few minute cysts. The cortex, which measures about 5 mm., is deep red. The glomeruli are conspicuous; the pyramids are injected. On the surface of the right kidney there is a yellow patch 0.5 cm. across (apparently aberrant adrenal tissue). Suprarenals together weigh 20 grams. They appear to be normal. The aorta is smooth save for a few slightly raised yellow patches. The urinary bladder is normal in size. Scattered over the inner surface, but chiefly on the posterior wall above the trigon, are submucous hemorrhages; in this situation are numerous minute vesicles. The rectum is deeply injected. The thyroid gland appears to be normal. The two parathyroids on either side were exposed, and as far as could be determined are normal. The small intestine in some places shows injection of the mucous membrane, most marked in the lower part of the ileum where the mucous membrane has a homogeneous, deep red color. The lumen of the appendix is patent. The large intestine throughout shows intense injection of the mucous membrane, but is otherwise negative.

Culture from the heart's blood shows a pure growth of Bacillus coli.

Microscopic Examinations. The liver tissue is much congested. The vessels of the kidney are all dilated and filled with blood. The epithelium of the tubules shows cloudy swelling; the cells are in places desquamated and the tubules are filled with debris. In the cortex there are many areas infiltrated with lymphoid cells. The bloodvessels of the lungs are everywhere congested, and in places there is serous exudate in the alveoli. There are many areas in which the alveoli are completely filled by polymorphonuclear leukocytes; there is a little fibrin. In several areas are chronic tuberculous lesions associated with newly formed fibrous tissue. The heart muscle is normal. The bloodvessels of the spleen are much congested.

Parathyroid Glands. The right and left superior parathyroid bodies were examined microscopically. They are of normal size and exhibit no abnormality. Scattered cells with affinity for eosin occur in moderate number. There is no increase of connective tissue and the bloodvessels are normal. The right inferior body likewise appears to be normal in structure and size. In the connective tissue near this parathyroid is a small round mass of tissue which resembles the much larger parathyroid body from which it is wholly isolated. The cells which compose this nodule are smaller than those of the parathyroid, and their protoplasm stains more deeply; they are, like those of the parathyroid, arranged in columns between the capillaries. About this nodule connective tissue is concentrically arranged to form an ill-defined capsule; in this tissue lymphoid cells are numerous. At a short distance from the nodule just described, and from the normal parathyroid and situated just outside the wall of a small vein, is an isolated round group of cells identical with those which make up the aberrant nodule. This group consists of about 25 small cells closely packed together. Sections made through the middle of the left inferior glandule showed that parathyroid tissue is abundant and normal. The parathyroid glands therefore, exhibit no abnormality; no evidence of hypertrophy is found. (Near one parathyroid are small aberrant nodules of tissue resembling that of the parathyroid.) The thyroid gland is normal in structure. The alveoli contain colloid in normal amount.

Studies of the Urine. Guinea-pig I. Injected with 20 c.c. of urine into peritoneal cavity. Died after twenty-four hours; some fluid in peritoneum. No exudate. Cultures sterile. Sections, see below.

Guinea-pig II. Injected with 15 c.c. of urine into peritoneal cavity. Died in thirty hours. Findings as in No. I.

Guinea-pig III. Injected with 10 c.c. of urine. Died in thirty-six hours. Findings as above. Three controls using normal urine, all recovered.

Studies of the Stomach Contents. Guinea-pig IV. Given 10 c.c. of filtered stomach contents by stomach tube; after twelve hours looked sick but recovered.

Guinea-pig V. Injected into peritoneal cavity 5 c.c. of filtered stomach contents. Died in ten hours—peritonitis. No convulsions. Cultures showed many organisms.

Guinea-pig I A. Injected 0.1 c.c. into peritoneum. Died in twelve hours. No convulsion. Anaërobic cultures of peritoneum, sterile.

Guinea-pig II A. Injected 0.2 c.c. subcutaneously. After eighteen hours it developed a paralysis of the right fore leg. Became very spastic, especially the hind legs; there was incoördination; no hyperesthesia, but stimulation of the abdomen caused clonic contractions of the limbs, which manifested itself in the jumping of the animal in a forward direction, which seemed uncontrollable. On several occasions the animal jumped so high as to strike on the top of the cage. After the spastic stage, a period of great weakness with loss of reflexes ensued, and the animal died in this stage twenty-two hours after injection.

Cultures. Aërobic: heart blood, Bacillus coli(?) spinal canal, Bacillus coli(?) Anaërobic: heart blood, Bacillus coli; spinal canal, sterile.

The abdominal parietes were very œdematous and reddened; no abscess formation; peritoneum and viscera normal. Brain and cord showed no macroscopic lesion.

Guinea-pig III A. 0.5 c.c. injected subcutaneously. This animal showed exactly the same symptoms as No. II A, except that the motor excitement stage was shorter, came on more quickly; died in twenty-one hours.

Cultures: Aërobic, as above; anaërobic, as above. Pathological findings, as above.

The microscopical sections of Guinea-pigs I, II, and III revealed marked cloudy swelling of the viscera; otherwise nothing of note was found.

Filtrate of Stomach Contents (Berkefeld Filter). Injected into guinea-pig as in I A, II A and III A; no apparent effect

Cultures of the filtrate revealed a few colonies of Bacillus coli.

It is a matter of regret that an examination of the brain and cord was not allowed, as the few reports of autopsies in cases of tetany are conflicting both as regards the existence of any constant lesion of the nervous system and its form. The full anatomical report on the parathyroid bodies, by Dr. Opie, is of especial interest.

Certain facts stand out prominently in the clinical study of the case which has been related:

1. The rapid and controlling effect of the soluble calcium salts upon the tetanic symptoms.
2. The maintenance of this effect only by their continued use.
3. The comparatively slight effect of large infusions of salt solutions, used alone.
4. The slight influence, if any, of parathyroid preparations (nucleoproteid) given by the mouth in controlling the hyperexcitability of the nervous system. The effect of the nucleoproteid given subcutaneously cannot be estimated positively in the present instance, as it was given alone only during a period of twenty-four hours and when the tetanic symptoms had been controlled practically by the calcium salt. A distinct renewal of the spasm at the end of this interval led to the renewed use of the calcium salt in combination with the parathyroid material. The demonstration of the controlling influence of the soluble calcium salts upon the characteristic

symptoms of at least one important variety of human spontaneous tetany—the tetany of gastrectasis, with stagnating stomach contents—suggests a probable similar therapeutic value of these salts in other forms of the disease in human beings.

5. The occurrence of typical tetanic spasm in a case of gastrectasis with parathyroid bodies of normal anatomical structure and—presumably—of normal functioning power.

The facts elicited in the clinical and pathological study of the cases add little to our positive knowledge of the pathogenesis of gastric tetany. A profound disturbance of the calcium metabolism would seem probable in the present instance. The explanation of it is difficult. There is much experimental evidence to show that the parathyroid secretion in some way controls the calcium exchange in the body, yet in the present instance the functioning power of the parathyroids presumably was normal. The generation of a poison of unknown nature in such amount as to cause a relative functional inadequacy of the parathyroid bodies can only be a matter of conjecture.

A COMMON MODIFICATION OF THE FIRST SOUND OF THE NORMAL HEART SIMULATING THAT HEARD WITH MITRAL STENOSIS.[1]

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Something like an apology seems due from one who ventures to attribute to trite and familiar phenomena a meaning beyond that which is offered by the consensus of scientific opinion. Yet the adept in auscultation knows that the net value of his examination involves no less the neglect of adventitious sounds than the appreciation of those which are of diagnostic worth. Therefore physical signs which pass unnoticed because devoid of meaning at once attract attention when they are found to imply an important modification of vital activity.

It is the design of the present contribution to direct attention to a modification of the first sound of the heart which allies it qualitatively to the first sound as heard in mitral stenosis, but which predicates no organic lesion. I venture to suggest that the light recently thrown by physiologists on the nature and variations of blood flow within the normal heart may be directed to the illumi-

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